2016–2017 Influenza Season Activity and Recommendations for Clinicians

Clinician Outreach and Communication Activity (COCA) Conference Call

February 16, 2017

National Center for Immunization & Respiratory Diseases
Influenza Division

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Objectives

At the conclusion of this session, the participant will be able to:

- Describe the current status of influenza activity in the United States.
- Explain the circulating influenza strains seen this season and the implications for clinicians.
- Discuss antiviral treatment of influenza and implications for patient evaluation, testing, and treatment.

Today's Presenters

Alicia Budd, MPH

Epidemiologist

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Centers for Disease Control and Prevention

Today's Presenter

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Medical Officer

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Centers for Disease Control and Prevention

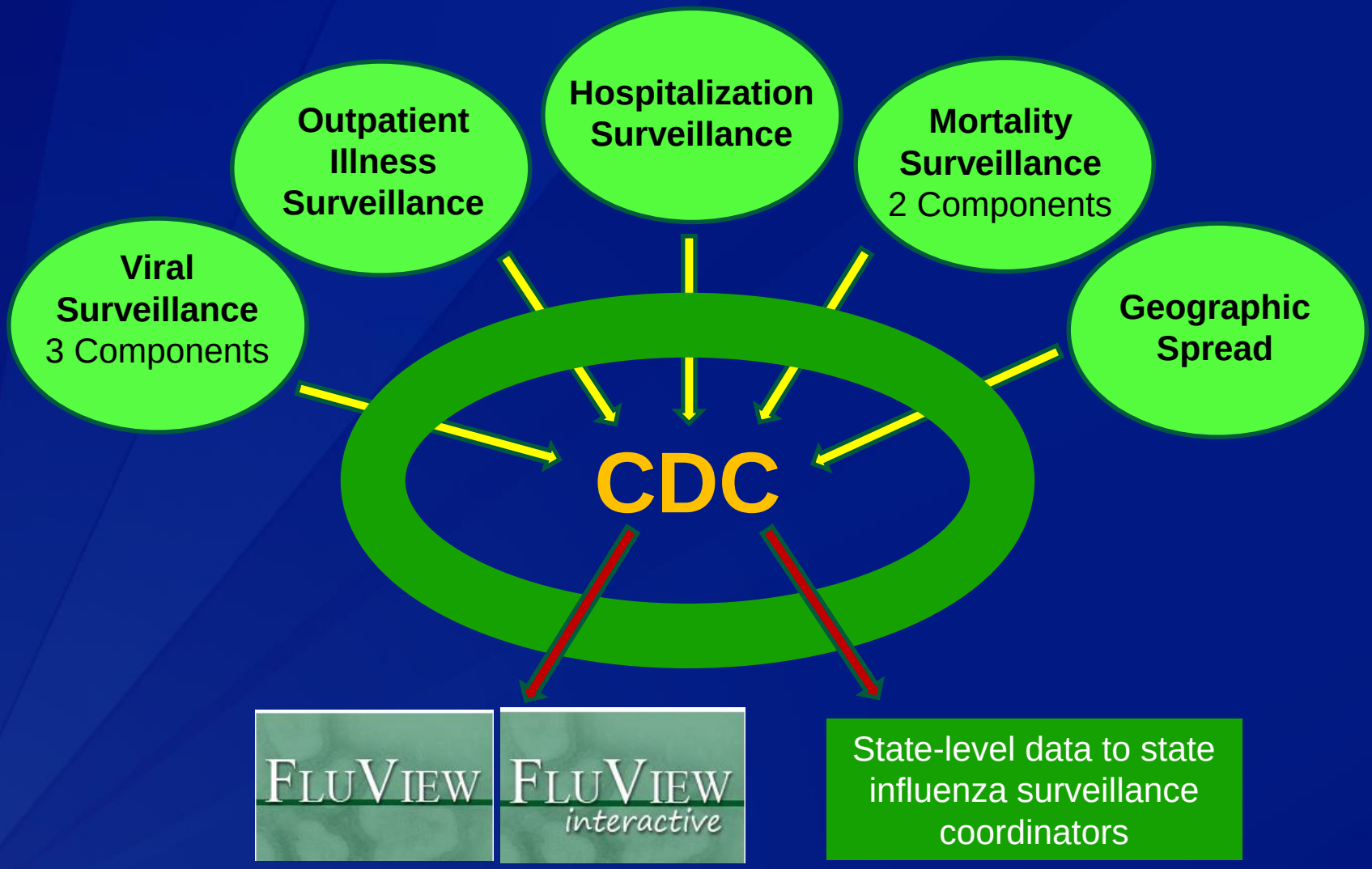
Outline

- Provide an update of the 2016–2017 influenza season
- Show interim estimates of influenza vaccine effectiveness
- Discuss influenza diagnostic testing
- Review CDC influenza antiviral recommendations

2016–2017 INFLUENZA SEASON

ACTIVITY THROUGH FEBRUARY 4, 2017

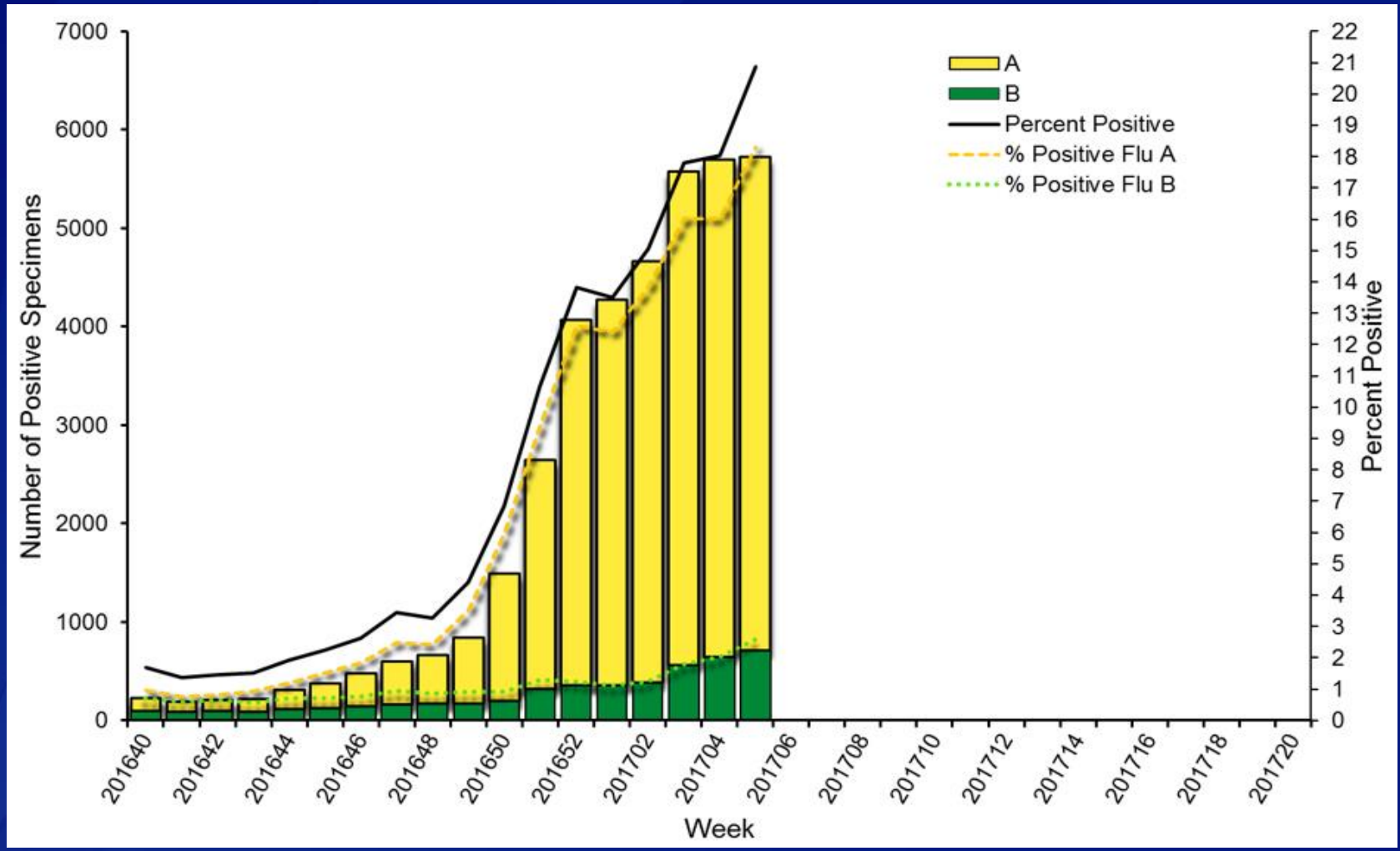
U.S. Influenza Surveillance System



U.S. Influenza Surveillance Reports

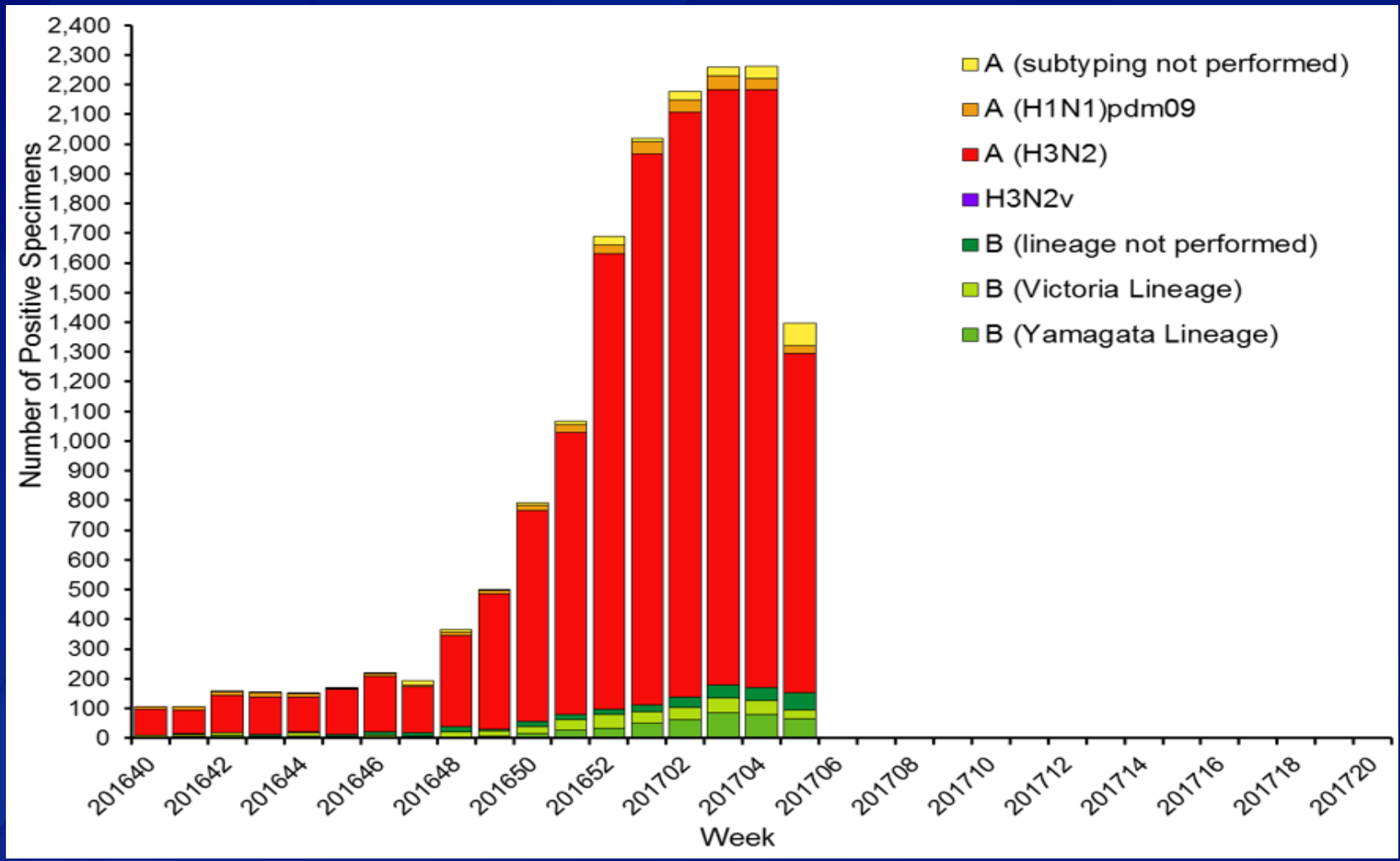
https://www.cdc.gov/flu/weekly/fluactivitysurv.htm

Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, 2016–2017 Season*



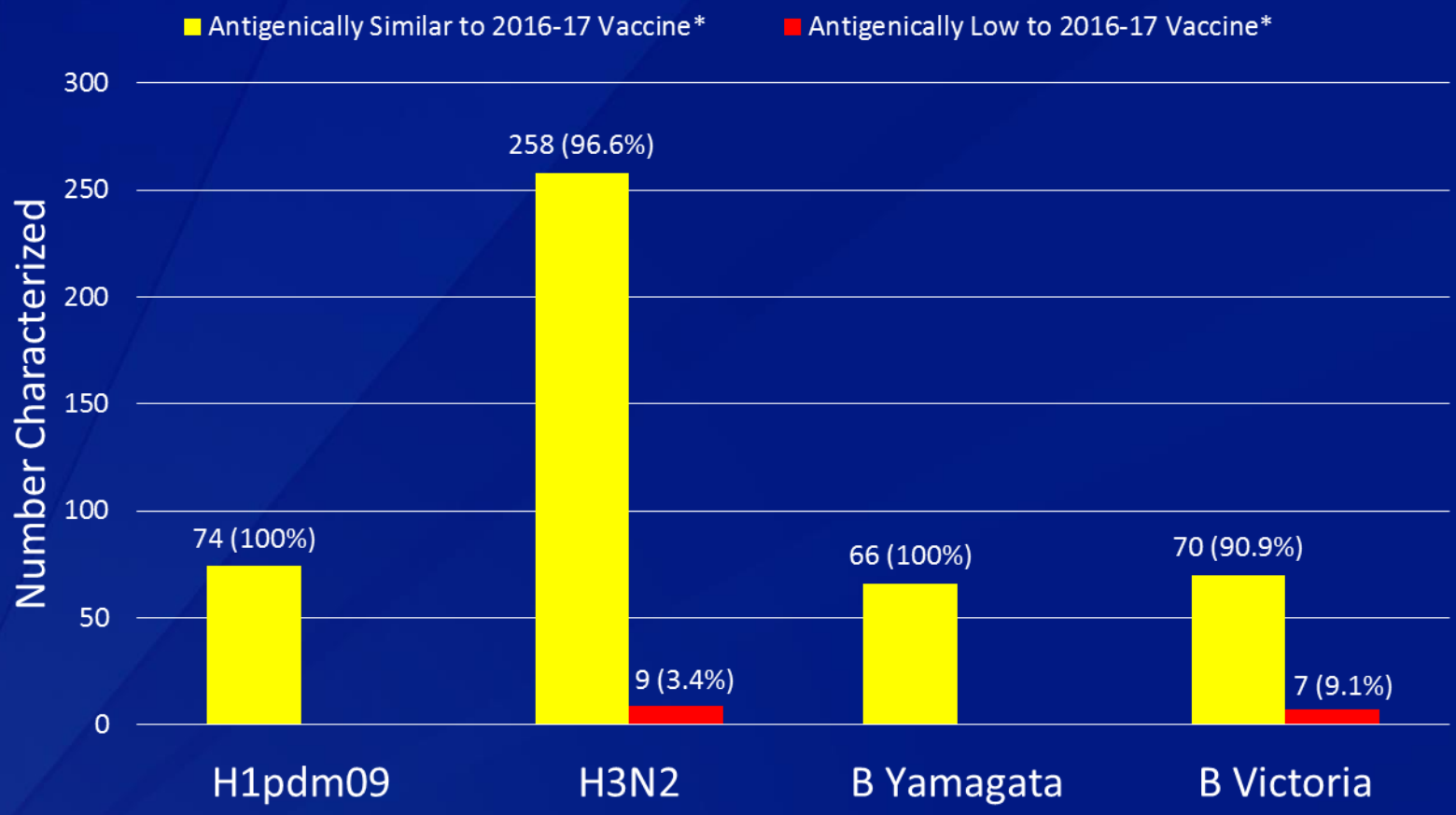
* As of February 10, 2017

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, 2016–2017 Season*



* As of February 10, 2017

Antigenic Characterization of U.S. Viruses Collected October 1, 2016 to present



*Against reference viruses representing NH 2016-2017 vaccine component

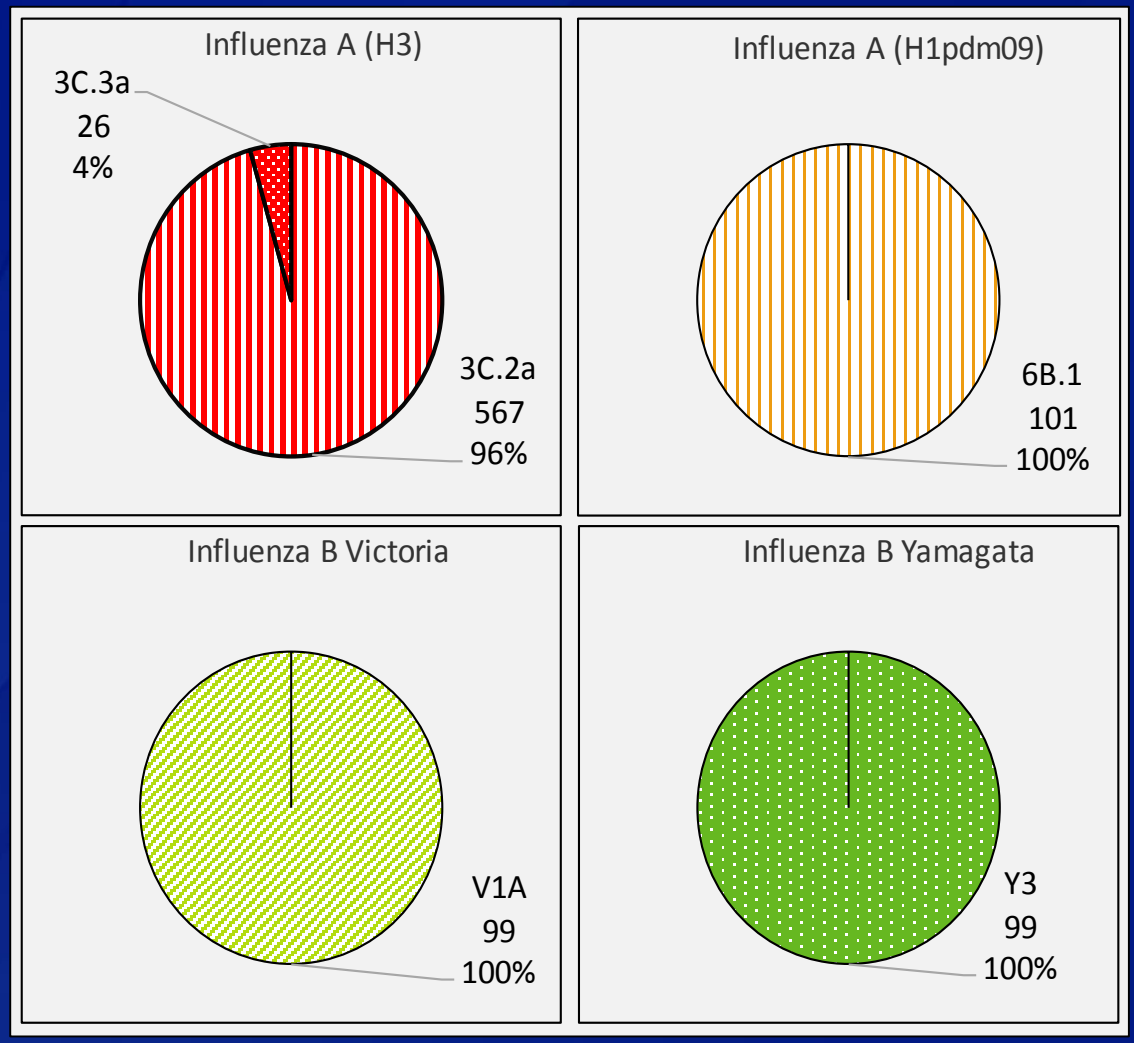
A(H1N1)pdm09 - A/California/07/2009

A(H3N2) – A/Hong Kong/4801/2014

B/Vic – B/Brisbane/60/2008

B/Yam - B/Phuket/3073/2013 (quadrivalent vaccine only)

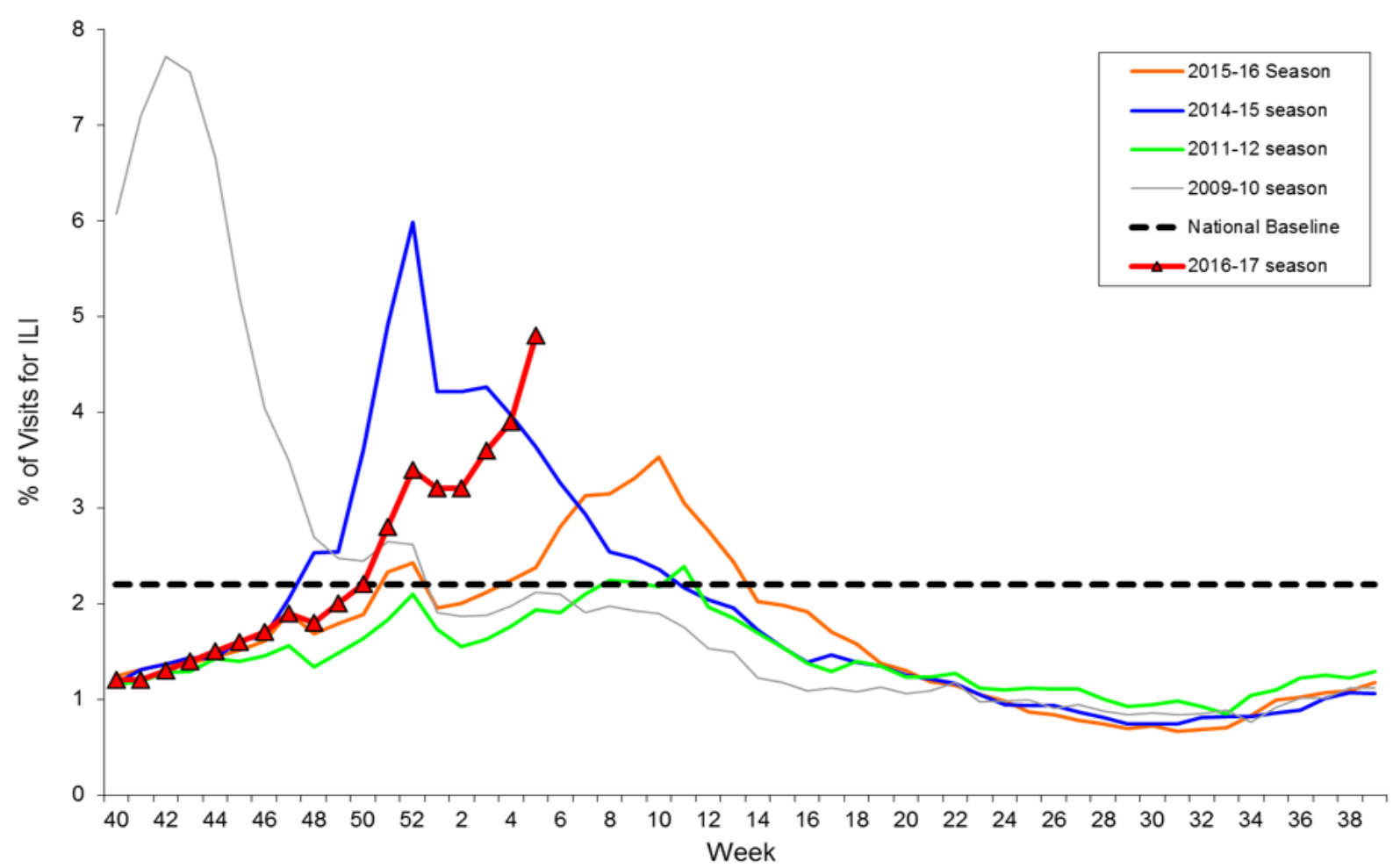
Genetic Characterization of U.S. Viruses Collected October 1, 2016 to present



Novel Influenza A Virus Infection: United States, 2016–2017 Season

- **Human infection with an influenza A virus that is different from currently circulating human seasonal viruses**
- **Influenza A (H1N2)v – Iowa**
  - Not hospitalized, fully recovered
  - Close contact with swine in week prior to illness onset
  - No human-to-human transmission
- **Influenza A (H7N2) – New York City**
  - Not hospitalized, fully recovered
  - Close, prolonged, unprotected exposure to sick cats infected with H7N2
  - No human-to-human transmission
  - First H7N2 infection in humans in the U.S. since 2003
  - First known human infection with an influenza virus likely acquired through exposure to a cat

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient ILI Surveillance Network (ILINET), 2016–2017* and Selected Previous Seasons

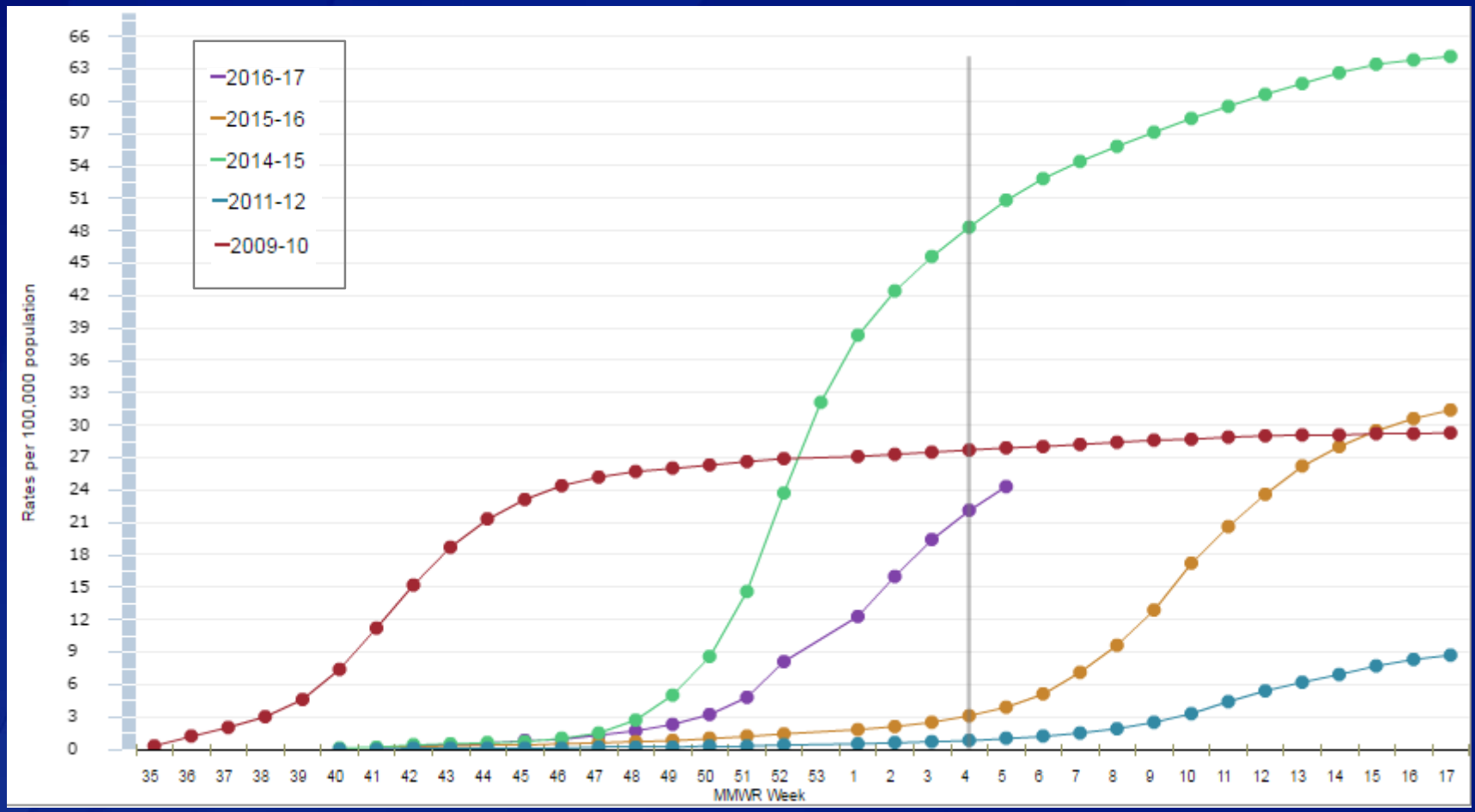


* As of February 10, 2017

Influenza-Like Illness (ILI) Activity Level Indicator Determined by Data Reported to ILINET,

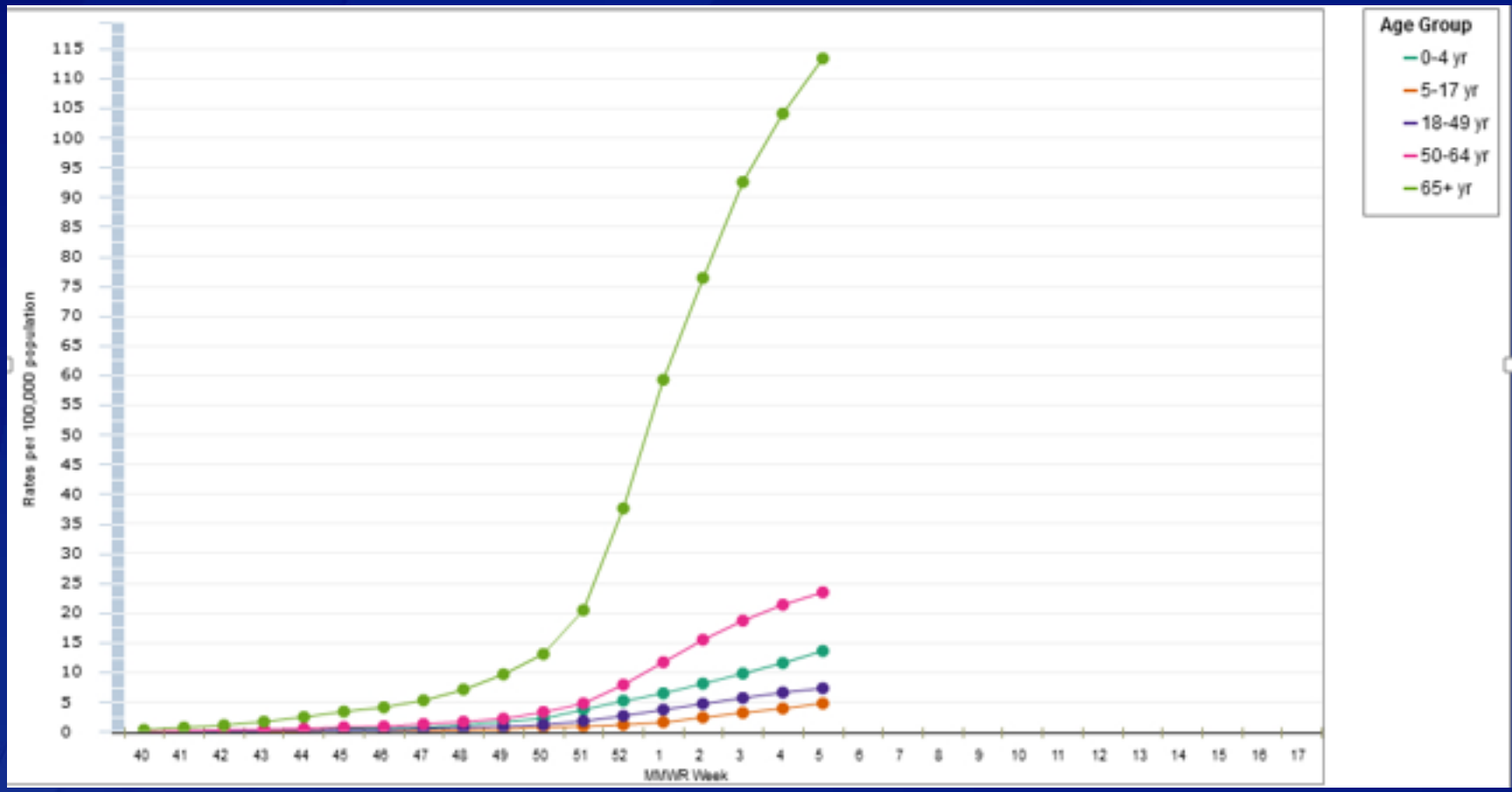
Week Ending February 4, 2017

Laboratory-Confirmed Influenza-Associated Hospitalizations, 2016–2017* and Selected Previous Seasons



* As of February 10, 2017

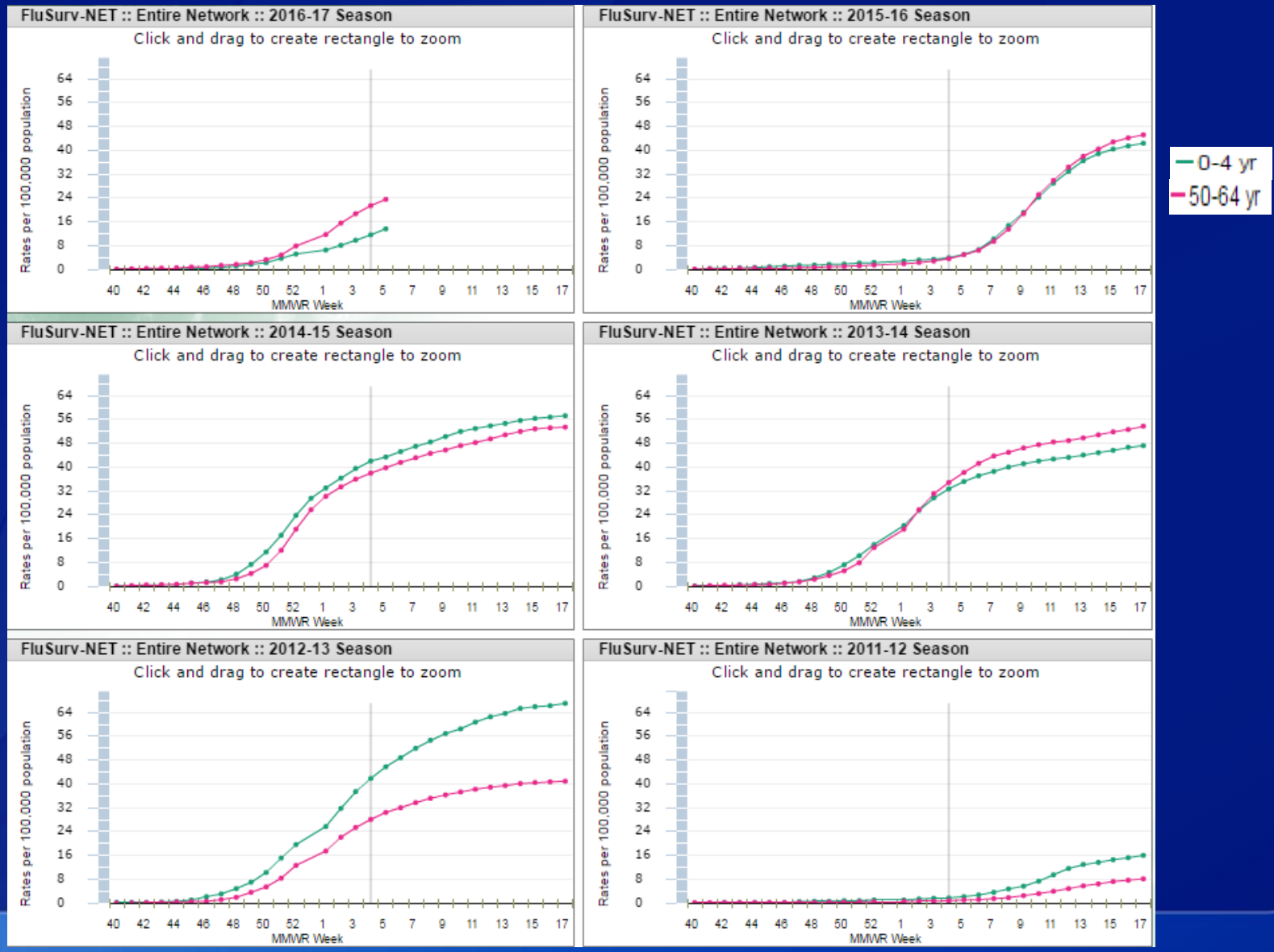
Laboratory-Confirmed Influenza-Associated Hospitalizations Preliminary* Cumulative Rates for 2016–2017 Season, by Age Group



* As of February 10, 2017

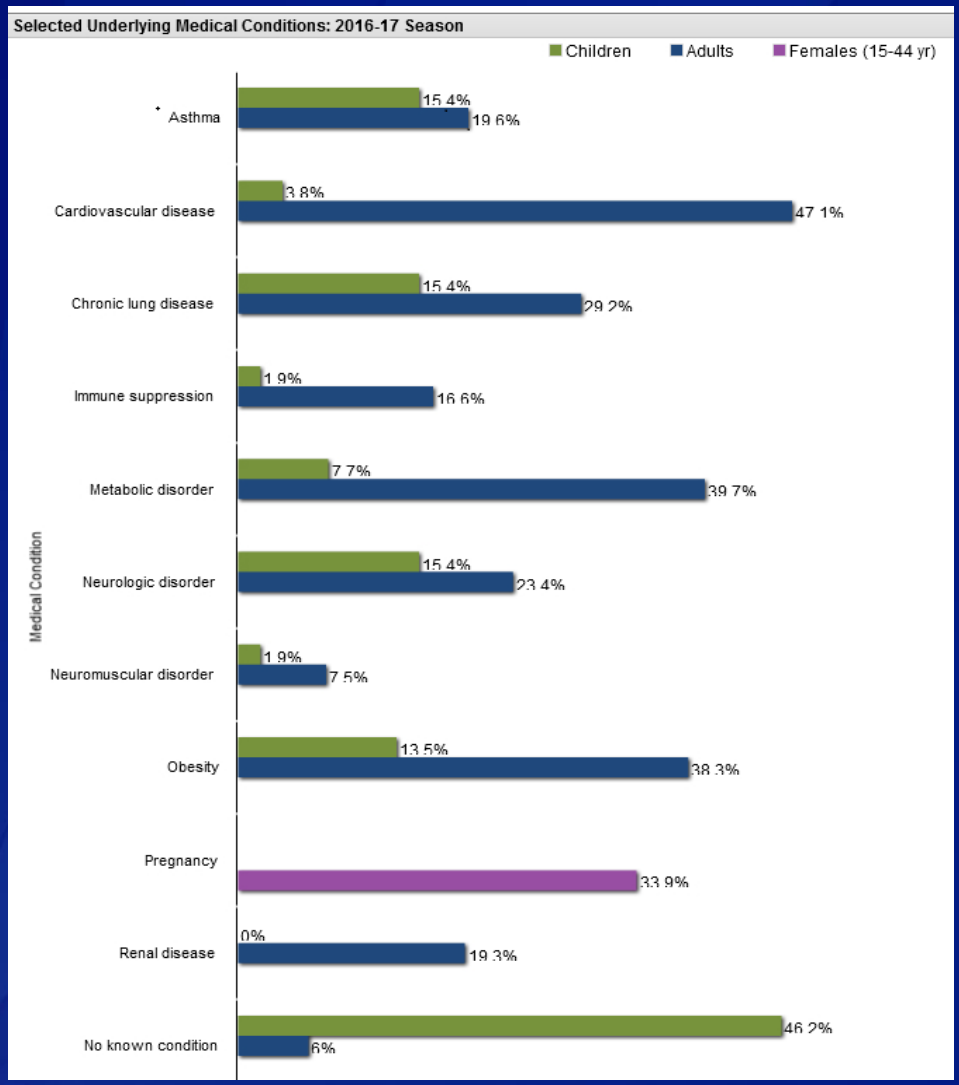
Laboratory-Confirmed Influenza-Associated Hospitalizations,

0-4 years and 50-64 years; 2016–2017* and Previous Five Seasons



* As of February 10, 2017

Laboratory-Confirmed Influenza-Associated Hospitalizations, Selected Underlying Medical Conditions, 2016–2017 Season*



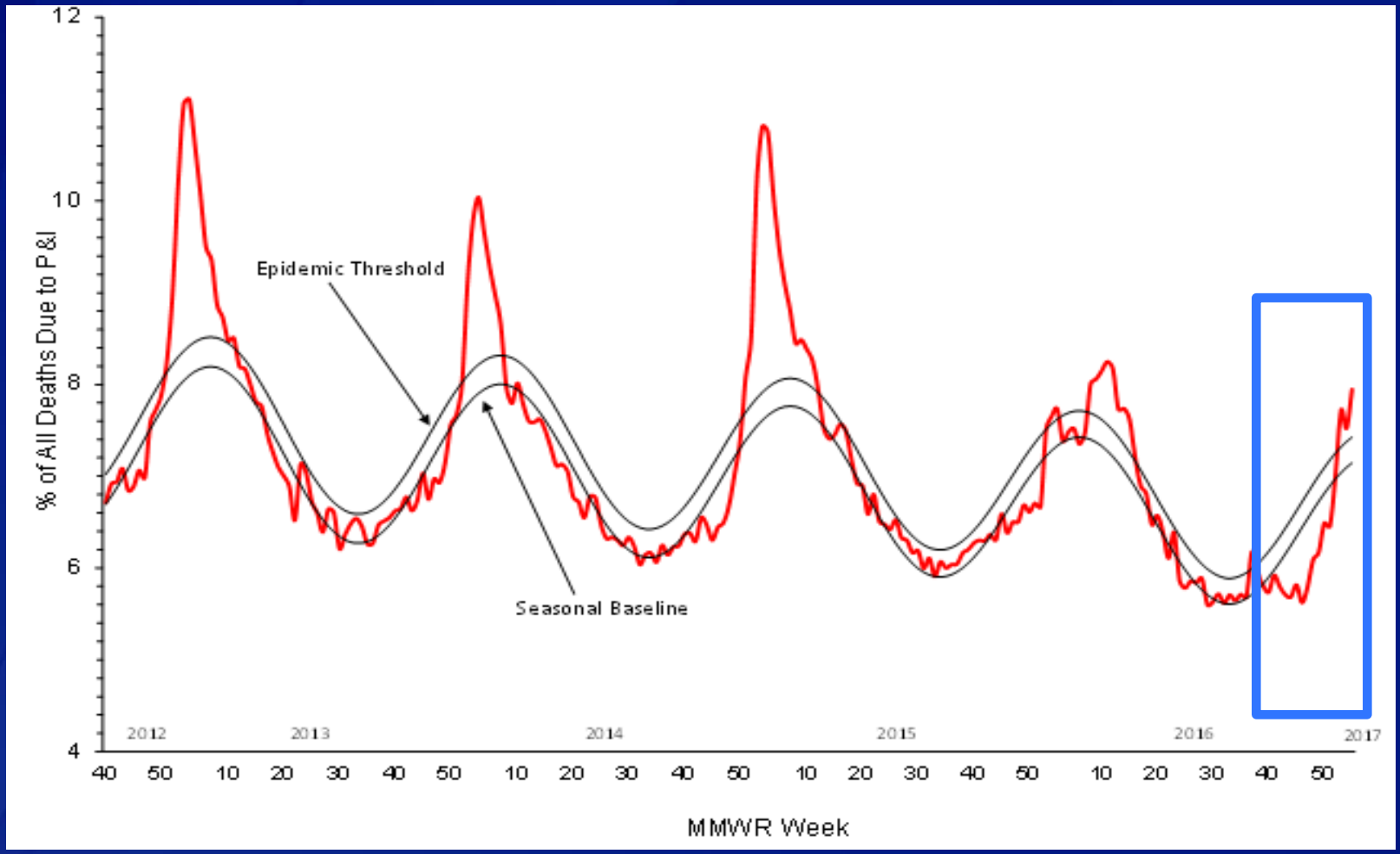
Any Reported Underlying Condition

- **95% of adults**
- **54% of children**

* As of February 10, 2017

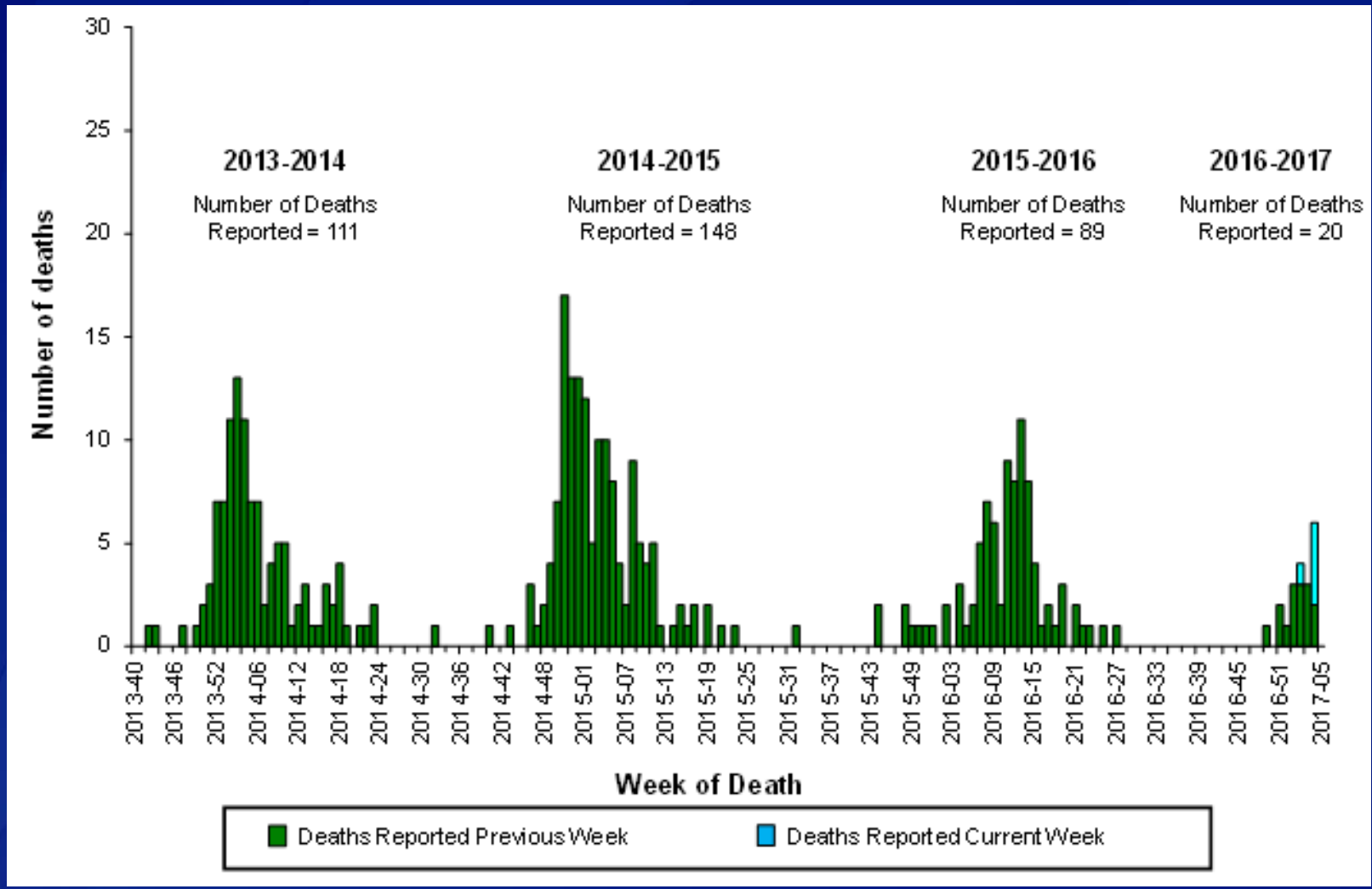
Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending January 21, 2017*

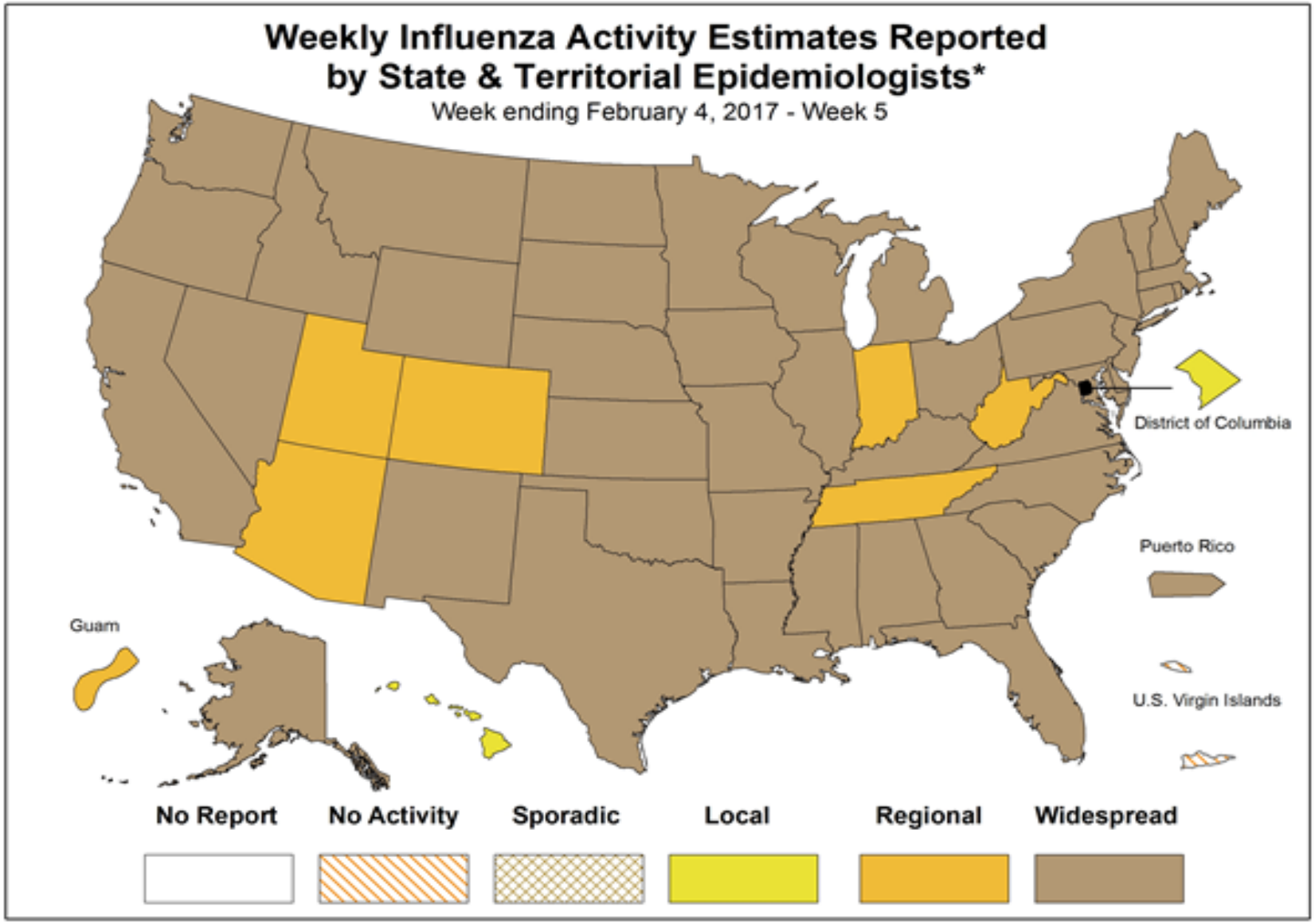


* As of February 10, 2017

Influenza-Associated Pediatric Deaths, by Week of Death: 2013-2014 Season to Present*

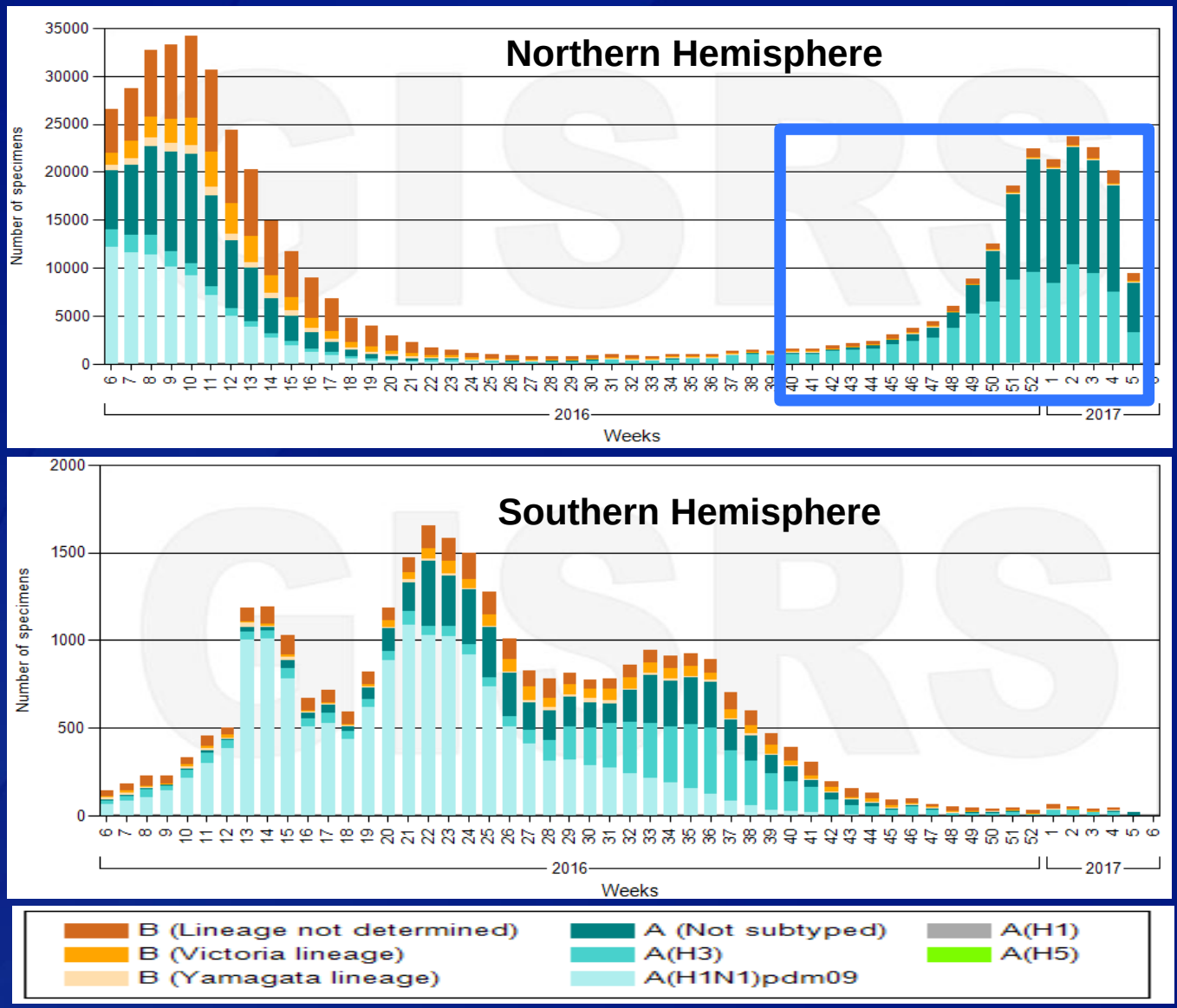


* As of February 10, 2017



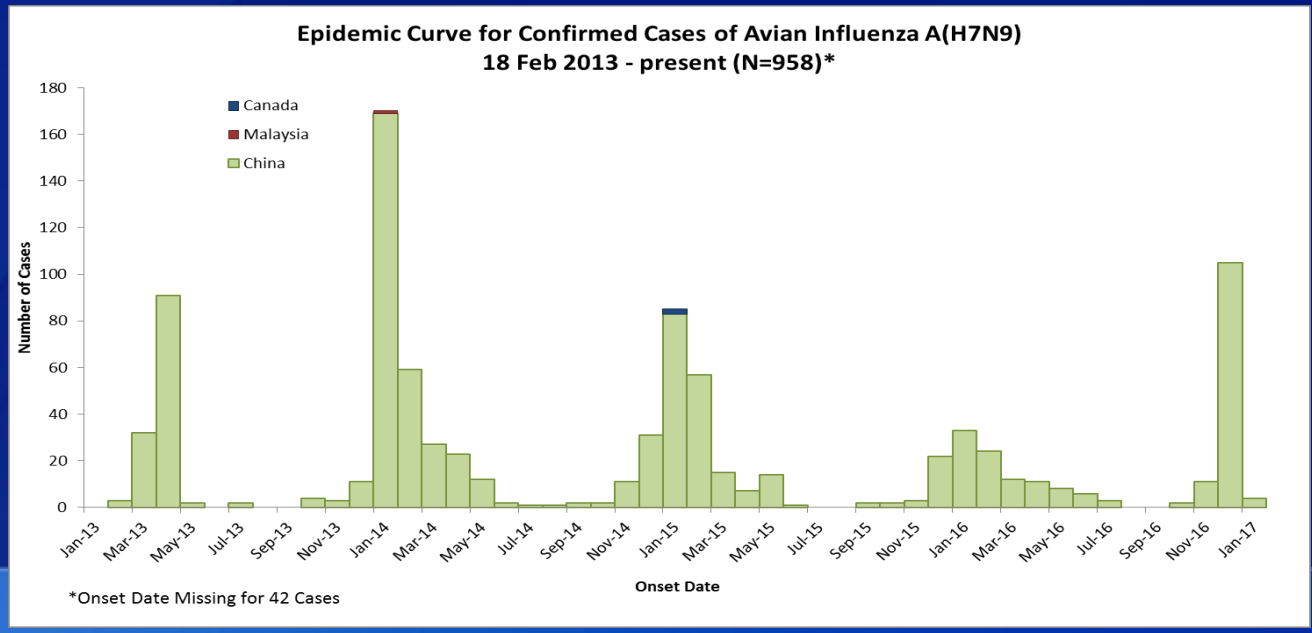
* This map indicates geographic spread & does not measure the severity of influenza activity

International Influenza Activity: Overview



International Influenza Activity: Novel Influenza A Virus Infection (1)

- **Influenza A (H7N9)**
  - Since 2013 China has had annual epidemics of human infection with avian influenza A (H7N9)
  - Most infections occurred after exposure to poultry
  - No evidence of sustained person-to-person transmission
  - Isolated reports of cases in other countries among travelers returning from China



International Influenza Activity: Novel Influenza A Virus Infection (2)

- Sporadic cases of human infection with other novel influenza A viruses have been reported.
- Avian influenza A (H5) viruses have been identified in wild and captive birds and domestic poultry in many countries.

Novel Influenza A Virus Infection: What You Can Do

- **Consider the possibility of infection with a novel influenza A virus in persons with**
  - ILI or ARI AND
  - Recent (<10 days prior to illness onset) contact with
    - Sick or dead domestic poultry or
    - Wild aquatic birds or
    - Captive birds of prey that have had contact with wild aquatic birds or
    - Sick swine

  - OR -

  - A respiratory specimen that cannot be typed or subtyped
- **Notify public health**
- **More information**
  - Avian influenza https://www.cdc.gov/flu/avianflu
  - Swine/Variant influenza https://www.cdc.gov/flu/swineflu

Summary: 2016–2017 Influenza Season*

- **Activity began to increase in mid-December and remains elevated through early February.**
- **Influenza A(H3N2) viruses are the most frequently identified viruses so far this season.**
  - H3N2 predominant seasons are often associated with higher mortality and hospitalization rates among older adults and young children.
- **Majority of viruses were characterized antigenically or genetically as being similar to the reference viruses representing vaccine components recommended for the 2016-17 influenza vaccine.**
- **Consider the possibility of novel influenza A virus infection in ill persons with recent travel history and/or exposure to ill animals.**

* As of February 10, 2017

VACCINATION AND INTERIM ESTIMATES OF VACCINE EFFECTIVENESS

Influenza Vaccination Recommendations

- The Advisory Committee on Immunization Practices (ACIP) recommends annual vaccination for all persons ≥6 months of age (since 2010–2011 season)

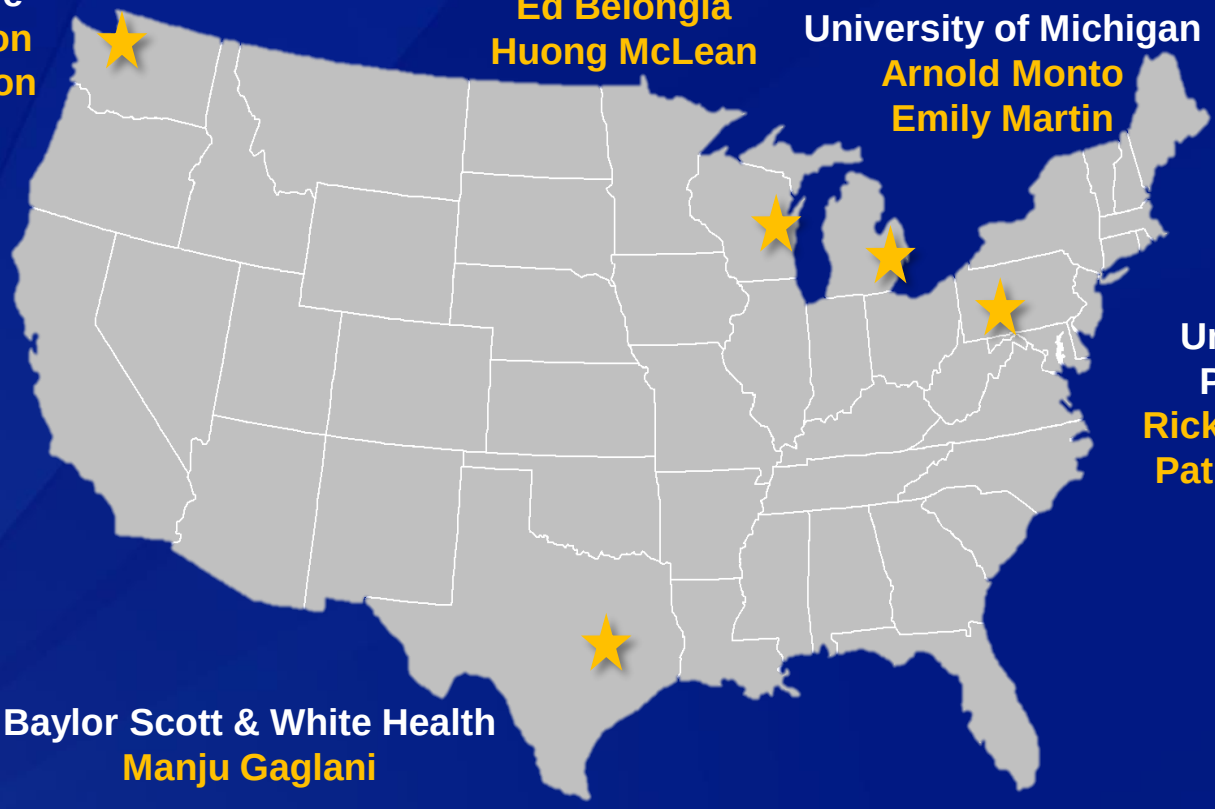
2016–2017 ACIP Prevention and Control of Seasonal Influenza with Vaccines

- **MMWR August 26, 2016**
- **Principal changes**
  - LAIV not recommended during the 2016-17 season because of concerns regarding low effectiveness against influenza A(H1N1)pdm09 during the 2013-14 and 2015-16 seasons
  - New/recent vaccine licensures
  - Changes to egg allergy recommendations
- **"What's New for the 2016–2017 Flu Season: Recommendations for Children" COCA Call 10/27/17**

  https://emergency.cdc.gov/coca/calls/2016/callinfo_102716.asp

Grohskopf L, et al. 2016; MMWR 65(5);1-54

US Flu VE Network
Sites and Principal Investigators



US Flu VE Network Methods

Enrollees: **Outpatients aged ≥6 months with acute respiratory illness with cough ≤7 days duration**

Dates of enrollment: **November 28, 2016 – February 4, 2017**

Design: **Test-negative design**

- Comparing vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls
- Vaccination status: receipt of at least one dose of any 2016–17 seasonal flu vaccine according to medical records, immunization registries, and/or self-report

Analysis: **VE = (1 – adjusted OR) x 100%**

- Adjustment for study site, age, self-rated general health status, race/Hispanic ethnicity, interval (days) from onset to enrollment, and calendar time

Interim Estimates of Vaccine Effectiveness against Medically Attended Influenza, 2016–2017

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Any influenza A or B virus	333/744	(45)	1317/2400	(55)	33	(21 to 44)	**48**	**(37 to 57)**
A/H3N2	282/595	(47)	1317/2400	(55)	26	(11 to 38)	**43**	**(29 to 54)**
B	23/90	(26)	1317/2400	(55)	72	(54 to 83)	**73**	**(54 to 84)**

*** Multivariate logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.**

Flannery B, et al. MMWR 17 Feb 2017

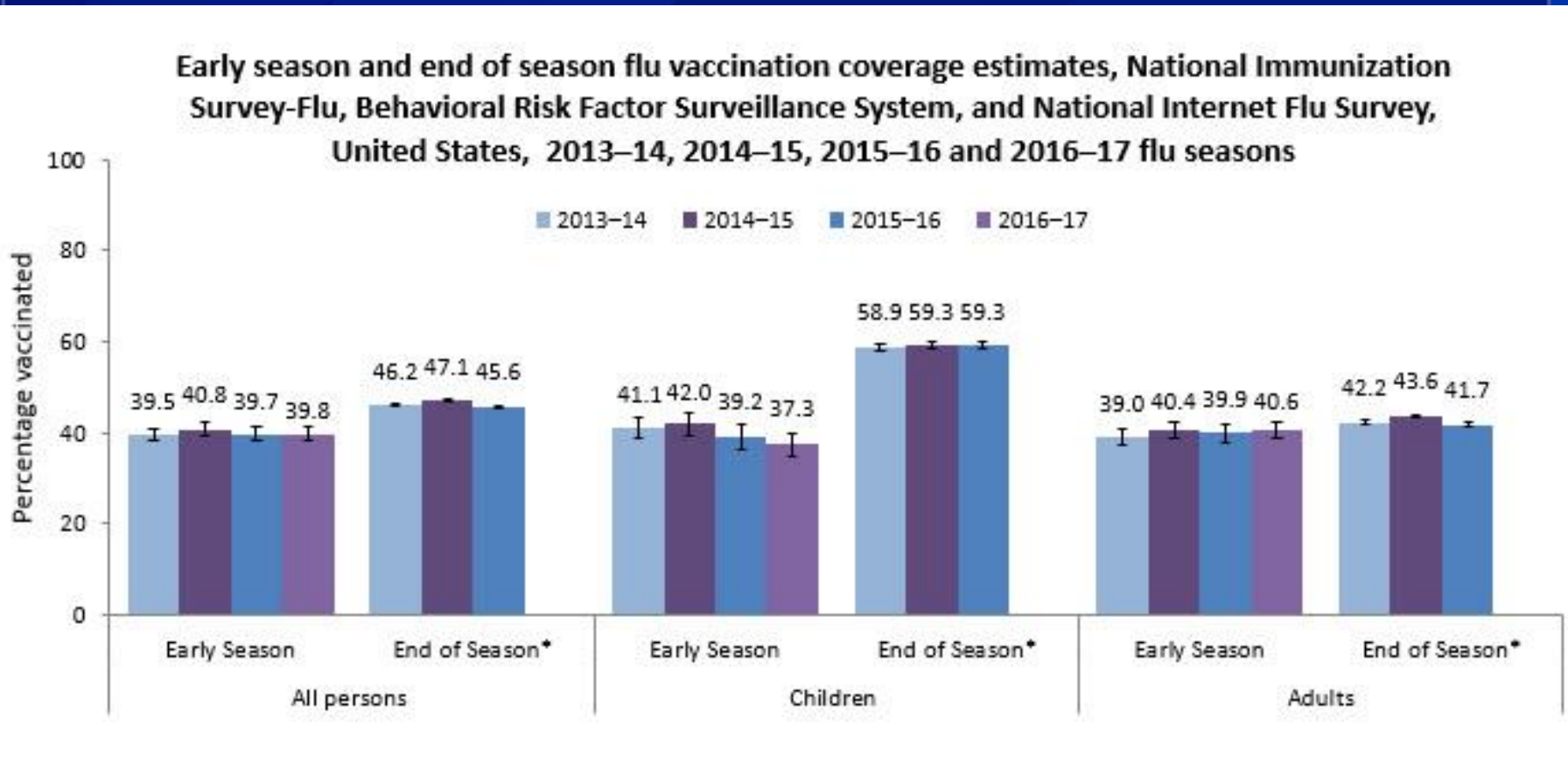
Pooled VE Estimates for H3N2 Viruses from Meta-Analysis of Test-Negative Design Studies

	Pooled VE (%)	Pooled standard error	VE estimates (n)*	p value for heterogeneity	I^2
H3N2 by season					
2010–11	46% (30 to 58)	0·131	5	0·368	26·1
2011–12	32% (23 to 40)	0·063	9	0·626	0·0
2012–13	40% (32 to 46)	0·059	6	0·644	0·0
2013–14	10% (–25 to 35)	0·164	3	0·913	0·0
2014–15	7% (–32 to 34)	0·179	3	0·051	74·3
H3N2 by antigenic similarity					
Variant	23% (2 to 40)	0·126	6	0·081	55·6
Similar	33% (22 to 43)	0·080	12	0·014	56·1

Table 4: Pooled VE estimates by season and reported antigenic similarity of H3N2 viruses to the vaccine strain

Belongia, et al. Lancet Infect Dis 2016;16:942-51.

National Early-Season Vaccination Coverage, November 2016



https://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2016.htm

Patient/Parent Resources

- **Misconceptions about Seasonal Flu and Flu Vaccines**
  - https://www.cdc.gov/flu/about/qa/misconceptions.htm
- **No More Excuses: You Need a Flu Vaccine**
  - https://www.cdc.gov/flu/pdf/freeresources/general/no-excuses-flu-vaccine-print.pdf
- **Common Vaccine Safety Concerns**
  - https://www.cdc.gov/vaccinesafety/concerns/
- **Parents' Guide to Childhood Immunizations**
  - https://www.cdc.gov/vaccines/parents/tools/parents-guide/parents-guide-part4.html

INFLUENZA DIAGNOSTIC TESTING

Influenza Testing in Clinical Settings

- **Accurate and prompt influenza diagnosis is important for clinical decision-making**
- **Variety of diagnostic tests available to clinicians to detect influenza viruses in respiratory specimens**
  - Differ by time to produce results, information provided, approved respiratory specimens, approved clinical settings, accuracy
    - Point-of-care assays (CLIA-waived)
    - Moderately complex (requires clinical laboratory)

Diagnostic Tests in Clinical Settings

- **Antigen detection (*low to moderate sensitivity*)**
  - Rapid influenza diagnostic tests (RIDTs)
    - Immunoassays (10-15 min to results)
    - Many CLIA waived
    - 50-70% sensitivity
  - Direct fluorescent antibody staining (DFA)
    - Requires fluorescent microscope (1-4 hr to results)
- **Molecular assays (*high sensitivity*)**
  - Rapid molecular assays (15-20 min to results)
  - RT-PCR assays (1-8 hr to results)

Influenza Virus Testing Methods

Influenza Virus Testing Methods

Table: Influenza Virus Testing Methods

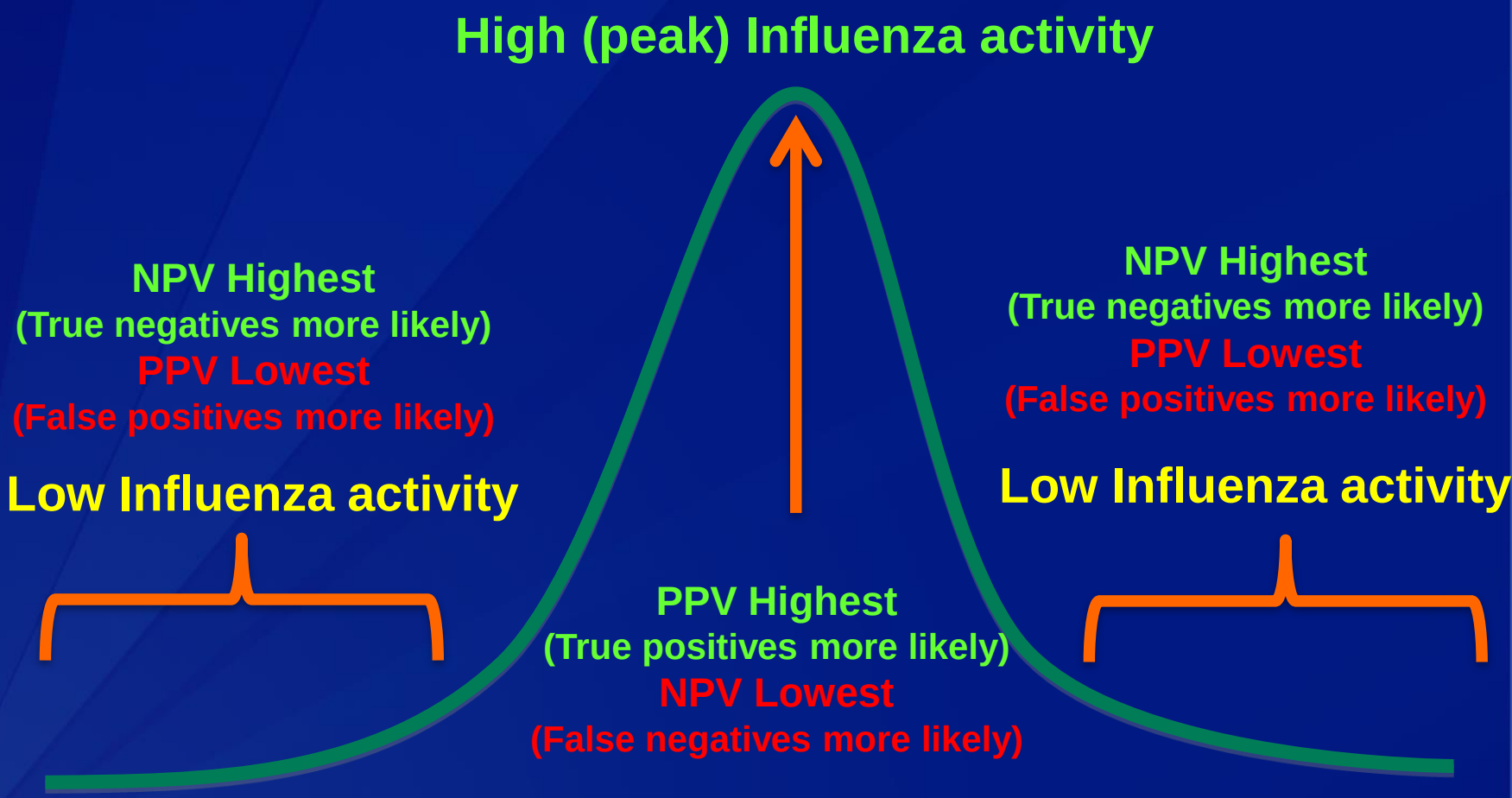
Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Rapid Influenza Diagnostic Tests[4] (antigen detection)	A and B	NP[5] swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	<15 min.	Yes/No
Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, nasal swab	<20 minutes[6]	Yes/No[6]
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining [antigen detection]	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[7] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (1 to 8 hours, varies by the assay)	No
Rapid cell culture (shell vials; cell mixtures; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum; (specimens placed in VTM[8])	1-3 days	No
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in VTM8)	3-10 days	No

https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm

Guidance for Influenza Diagnostic Testing

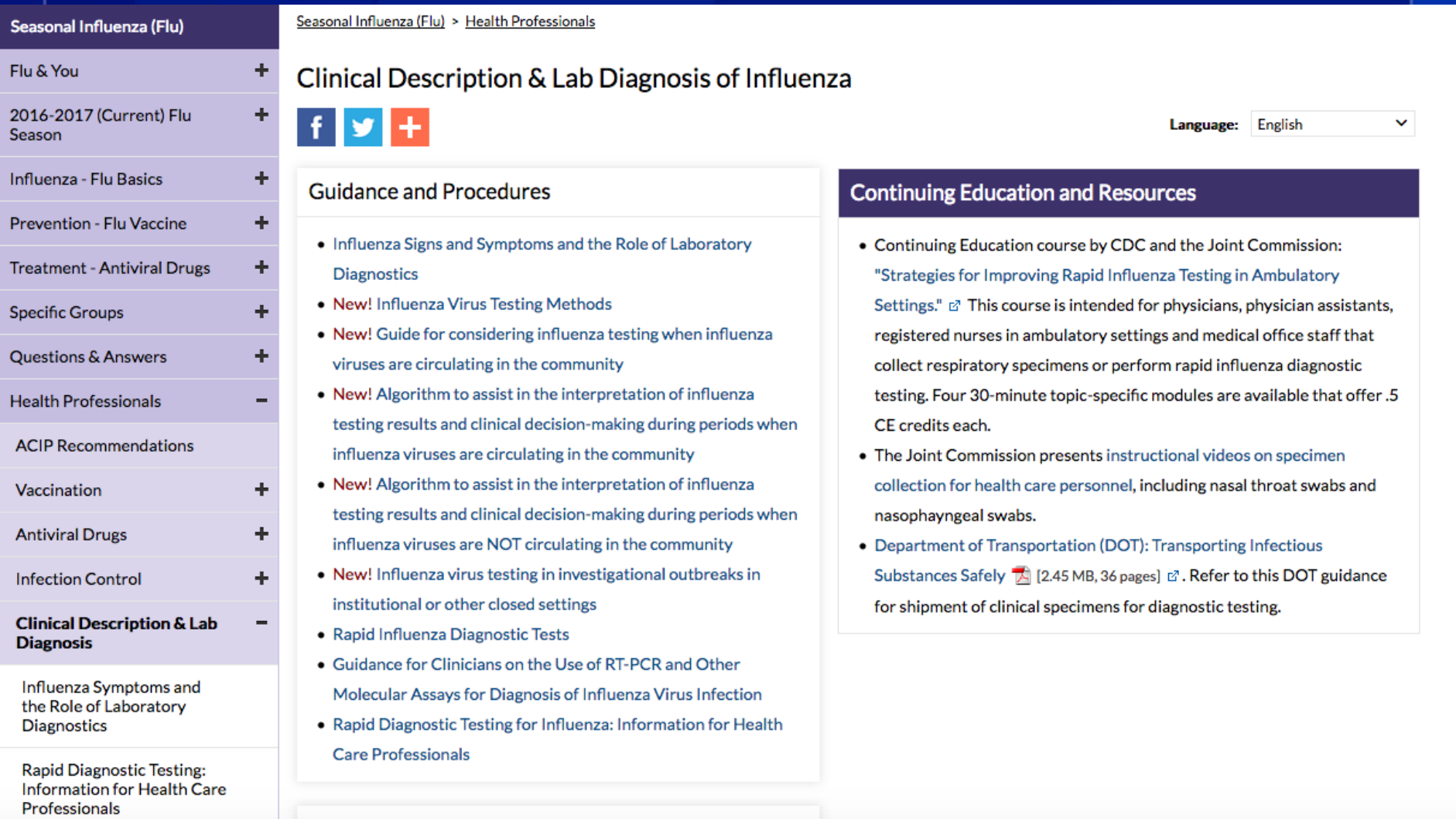
- **For immunocompetent patients, best to collect specimens <3-4 days from illness onset**
  - Prolonged viral replication in young infants, immunosuppressed, critically ill
- **Optimal respiratory specimens**
  - Upper respiratory tract (nasopharyngeal > nasal > throat)
  - Lower respiratory tract
    - Critically ill patients (may detect when viral shedding is not detectable in the upper respiratory tract)
- **Proper interpretation of testing results**
  - Consider false negative results

Prevalence (Influenza Activity) and Predictive Values of Influenza Tests



Uyeki T, Chapter 177; Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th Ed, 2013

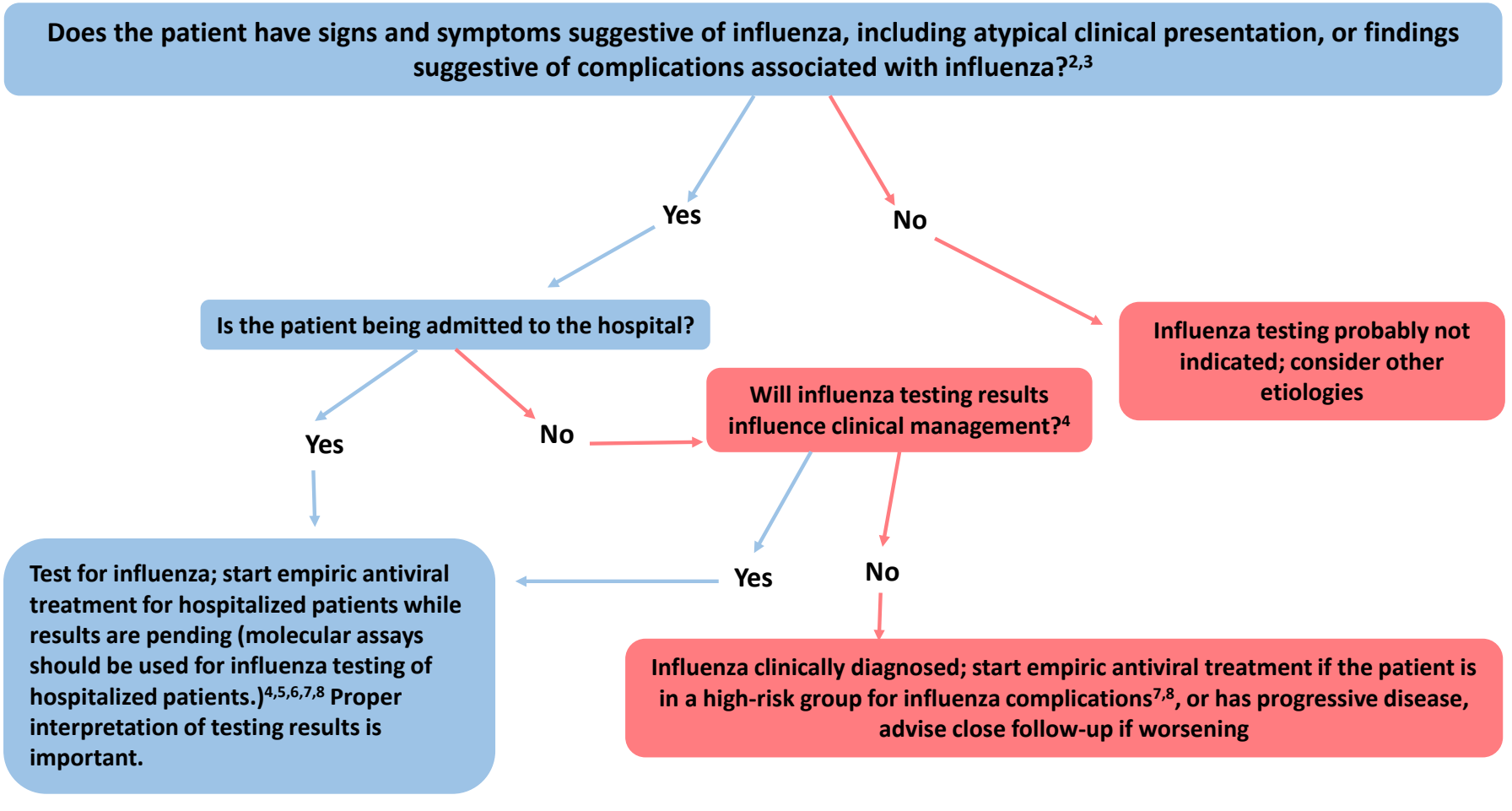
Updated Testing Guidance



https://www.cdc.gov/flu/professionals/diagnosis/index.htm

Guidance for Considering Influenza Testing

Figure: Guide for considering influenza testing when influenza viruses are circulating in the community (regardless of influenza vaccination history)[1]



https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm

INFLUENZA ANTIVIRAL RECOMMENDATIONS

Antiviral Medications for Influenza

- **Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine**
- **Three FDA-approved antivirals (all neuraminidase inhibitors) are recommended for use this season**
  - Oral oseltamivir (available as a generic version or under the trade name Tamiflu®)
    - Generic oseltamivir capsules were approved by FDA in August and became available in December, 2016
  - Inhaled zanamivir (trade name Relenza®)
  - Intravenous peramivir (trade name Rapivab®)

CDC Antiviral Guidance

- **Focus of CDC influenza treatment guidance is on *prevention of severe outcomes***
  - Treatment of those with severe disease and persons at highest risk of severe influenza complications
  - No RCTs available
- **Based on observational studies and meta-analyses of antiviral effectiveness**
  - Early treatment among hospitalized patients is associated with reduced mortality in adults and shortened length of stay in children and older adults
  - The earlier treatment is initiated, the better the outcomes
- **Antiviral recommendations are common to ACIP, IDSA, AAP**

Muthuri, Lancet Resp Med 2014;2:395-404; Lipsitch, CID 2013;57:1368-9;
Dobson, Lancet 2015; 385(9979):1728; Louie, CID 2012;55:1198-204; Yu, CID 2011;52:457-65

CDC Antiviral Recommendations (1)

- **All patients in the following categories with suspected or confirmed influenza should be treated *as soon as possible*, without waiting for confirmatory influenza testing**
  - Hospitalized patients
  - Patients with severe, complicated, or progressive illness
  - Patients at high risk for complications from influenza (either outpatient or hospitalized)

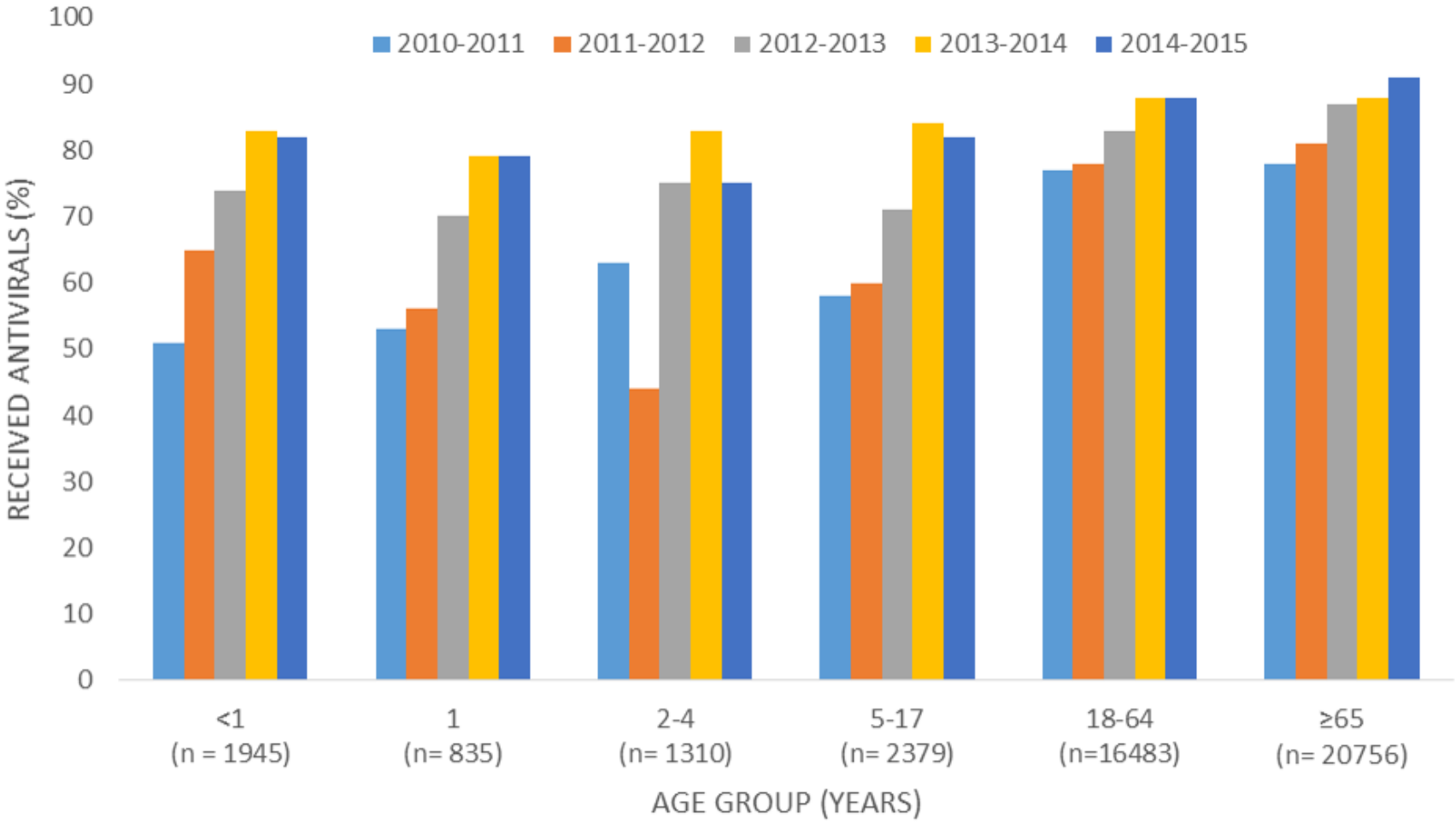
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

CDC Antiviral Recommendations (2)

- **Antiviral treatment also can be considered for any previously healthy (non-high risk) symptomatic outpatient with suspected or confirmed influenza on the basis of clinical judgment**
  - If treatment can be initiated within 48 hours of illness onset

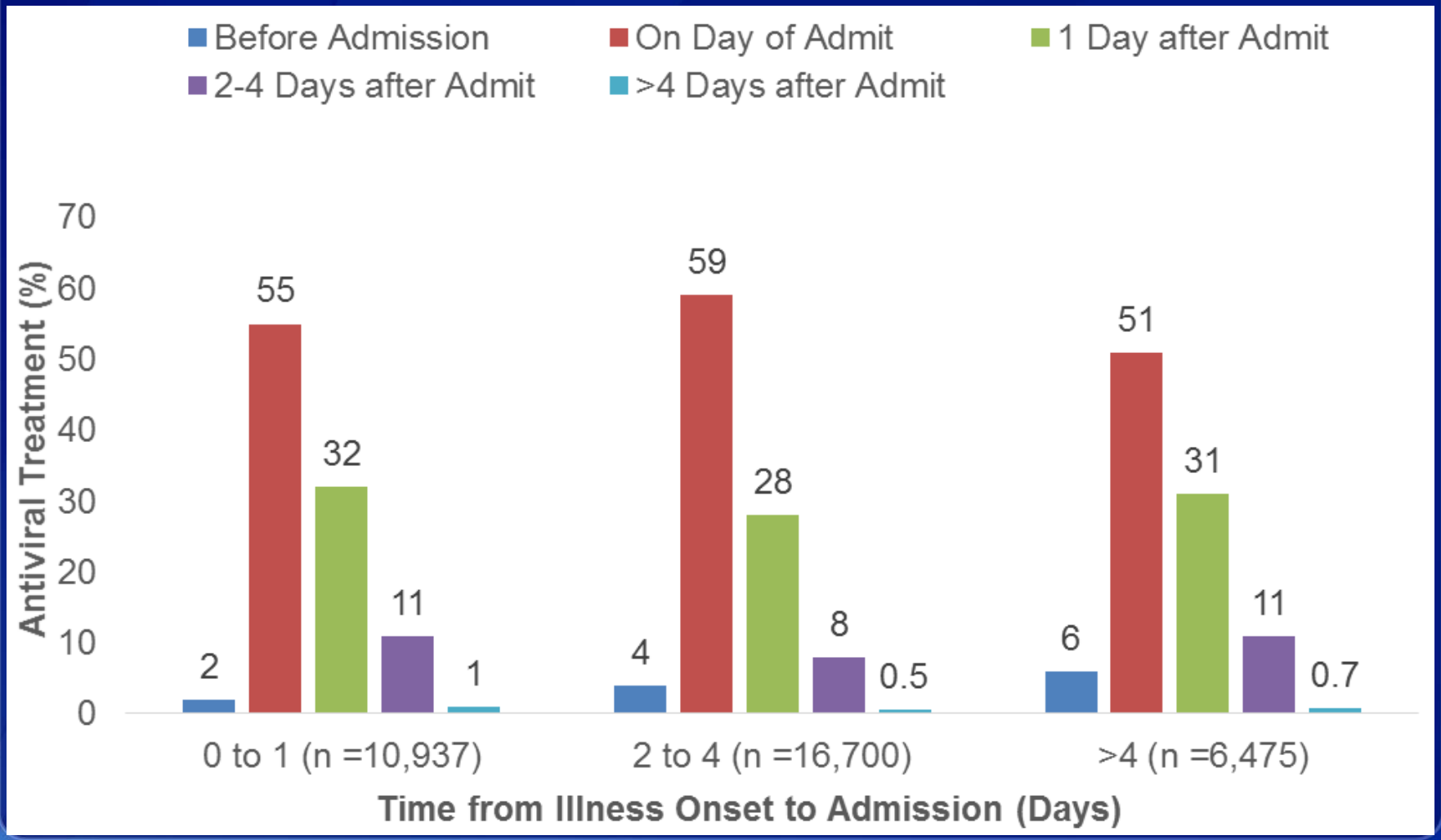
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Antiviral Treatment in Patients Hospitalized with Laboratory-Confirmed Influenza, FluSurv-NET



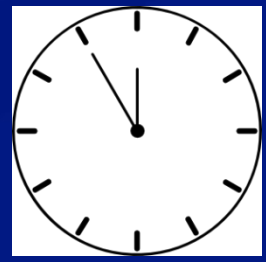
Appiah G, et al. Clin Infect Dis, 2017;64(3):364-67

Timing of Antiviral Treatment Relative to Hospital Admission, FluSurv-NET



Appiah G, et al. Clin Infect Dis, 2017;64(3):364-67

Timing of Treatment



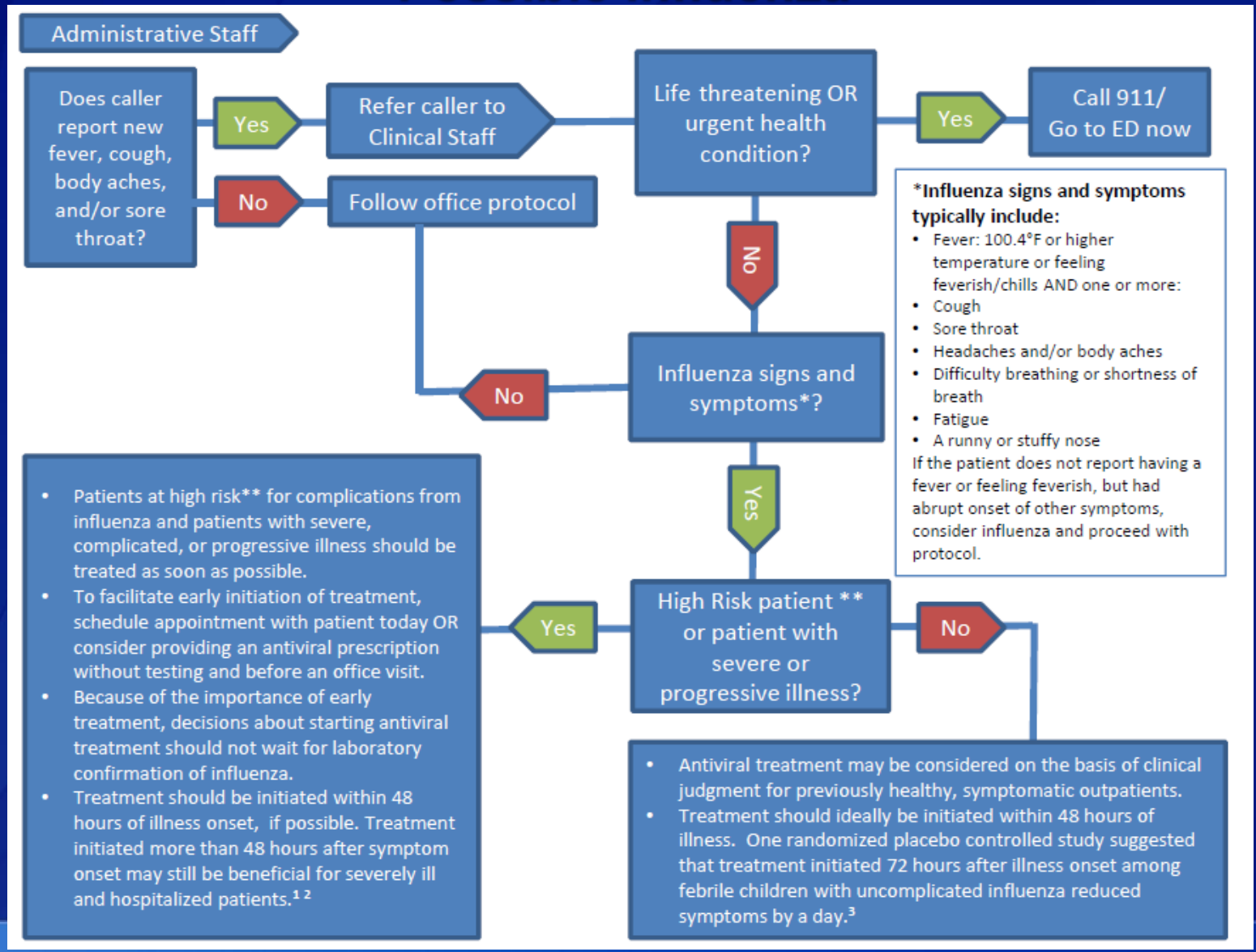
- **When indicated, antiviral treatment should be started as soon as possible after illness onset**
- **Ideally within 48 hours of symptom onset**
- **Treatment should not be delayed even for a few hours to wait for the results of testing**
  - A negative rapid influenza antigen diagnostic test does **not** exclude a diagnosis of influenza

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

High-Risk Outpatients and Early Treatment

- During influenza season, providers should advise high-risk patients to call promptly if they have symptoms of influenza
- Phone triage lines may be useful to enable high risk patients to discuss symptoms
- To facilitate early initiation of treatment, when feasible, an antiviral prescription can be provided without testing and before an office visit

Medical Office Telephone Evaluation of Patients with Possible Influenza



https://www.cdc.gov/flu/professionals/antivirals/office-evaluation.htm

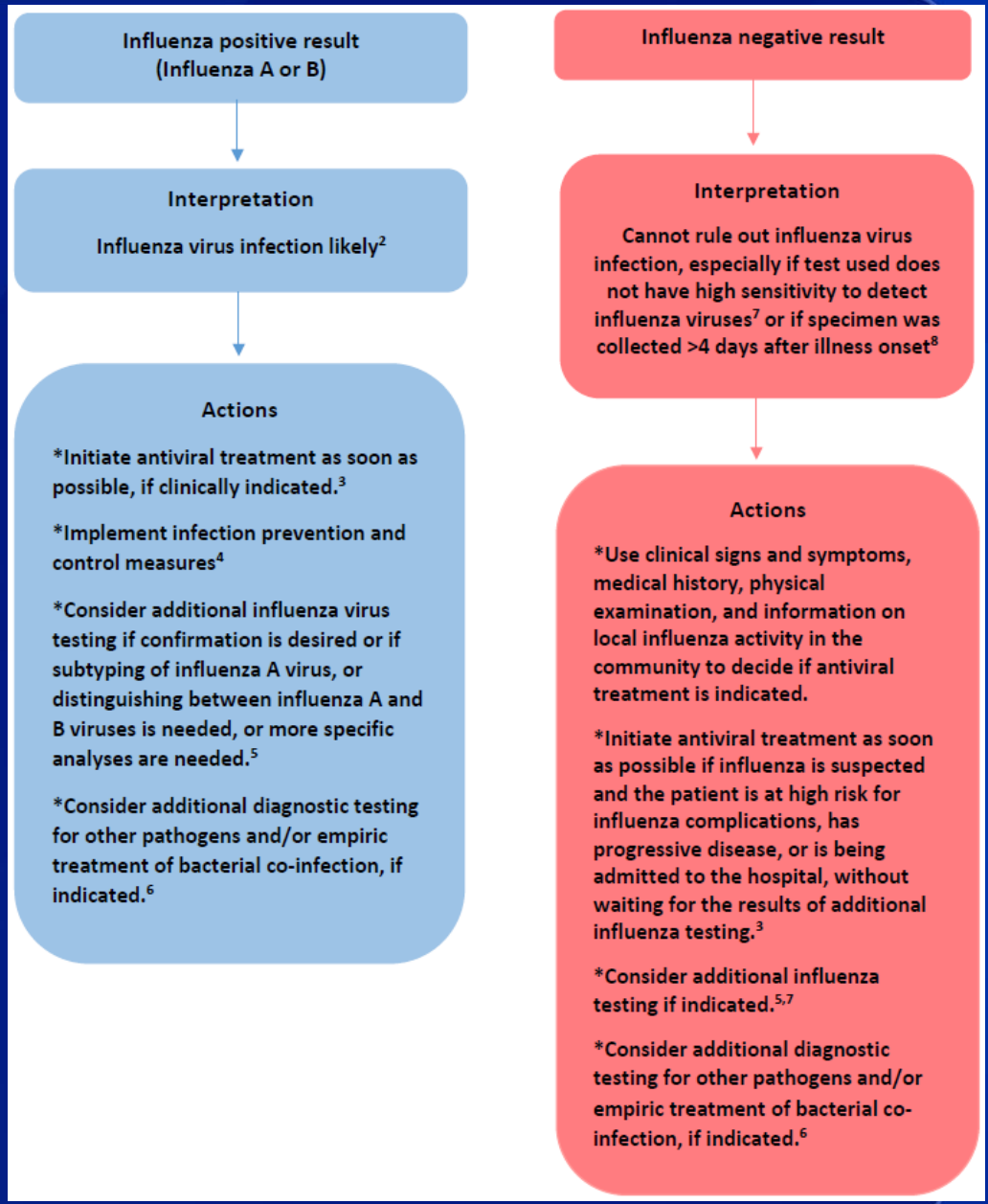
Antiviral Treatment Initiated after 48 Hours Can Still be Beneficial in Some Patients

- Observational studies of hospitalized patients suggest that treatment might still be beneficial when initiated 4 or 5 days after symptom onset
- Observational data in pregnant women has shown antiviral treatment to provide benefit when started 3-4 days after onset
- A randomized placebo controlled study suggested clinical benefit when oseltamivir was initiated 72 hours after illness onset among febrile children with uncomplicated influenza

Muthuri, Lancet Resp Med 2014;2:395-404; Louie, CID 2012;55:1198-204; Yu, CID 2011;52:457-65; Siston, JAMA 2010;303:1517-25; Fry, Lancet ID 2014;14:109-18

Algorithm to Assist in Interpretation of Testing Results and Clinical Decision Making

- When influenza viruses *are circulating* in the community



https://www.cdc.gov/flu/professionals/diagnosis/algorithm-results-circulating.htm

Outpatient Treatment

- **Any neuraminidase inhibitor may be used for treatment of outpatients**
  - 5-day course of oseltamivir (for all ages) or inhaled zanamivir (for age ≥7 years)
  - 1 dose of IV peramivir (for age ≥18 years)
- **Oral oseltamivir is preferentially recommended for pregnant women**

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment for Hospitalized Patients

- **Treatment with oral or enterically administered oseltamivir is recommended**
  - Limited data suggest that oseltamivir administered by oro/naso gastric tube is well absorbed in critically ill patients, including those in the intensive care unit, on continuous renal replacement therapy, and/or on extracorporeal membrane oxygenation
- **Inhaled zanamivir is not recommended because of lack of data for use in patients with severe influenza disease**
- **Insufficient data regarding efficacy of intravenous peramivir for hospitalized patients**
- **For patients who remain severely ill after 5 days of treatment, longer treatment courses may be considered**

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment for Hospitalized Patients:
Concern Regarding Oseltamivir Absorption

- **For patients who cannot tolerate or absorb oral oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of IV peramivir or investigational IV zanamivir should be considered**
  - In a randomized trial in hospitalized patients aged >6 yr, dose of IV peramivir was 600 mg IV once daily for 5 days (clinical benefit was not demonstrated)
  - Longer daily dosing for patients who remain severely ill can be considered

de Jong, et al. CID 2014; 59:172-85; Ison, et al. Antivir Ther. 2014;19:349-61

Treatment for Hospitalized Patients:
Concern Regarding Oseltamivir Resistance

- **Some influenza viruses may become resistant to oseltamivir and peramivir during antiviral treatment with one of these agents and remain susceptible to zanamivir**
  - Investigational use of intravenous zanamivir should be considered for treatment of severely ill patients with oseltamivir-resistant virus infection

Additional Information: Antibiotics and Bacterial Infections

- Antibiotics are not effective against influenza
- Several reports suggest inappropriate use of antibiotics for patients with influenza
- Bacterial infections can occur as a complication of influenza, so should be considered and appropriately treated if suspected

Institutional Outbreaks (1)
(Long-Term Care Facilities, Nursing Homes, other Living Facilities that House High-Risk Persons)

Influenza outbreak management requires a multi-faceted approach:

1. **Vaccination**
2. **Diagnostic Testing**
3. **Infection Control**
4. **Antiviral Treatment**
5. **Antiviral Chemoprophylaxis**

https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Institutional Outbreaks (2)
(Long-Term Care Facilities, Nursing Homes, other Living Facilities that House High-Risk Persons)

- **Use of antiviral chemoprophylaxis to control outbreaks among high-risk persons in institutional settings is recommended**
  - For all residents (regardless of vaccination status)
  - For unvaccinated healthcare personnel
  - For a minimum of 2 weeks, continuing at least 7 days after last known case identified

https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Antiviral Supply

- **No current national shortages**
  - Manufacturers have stated that they have sufficient product on hand to meet this season's projected demand

CDC Division of Strategic National Stockpile Antiviral Call Center

- For long-term care facilities or institutions experiencing difficulty accessing antiviral supplies in outbreak settings
- CDC will coordinate with commercial supply chain partners to rapidly redirect supply of large orders of antiviral drugs to the identified location
- Available from 8:00 AM to 5:00 PM EST, Mon–Fri, to assist public health officials and health care facilities
- Contact DSNS at dsns-Request@cdc.gov for assistance

Summary of Antiviral Recommendations

- **Early empiric antiviral treatment is recommended for suspected or confirmed influenza among the following:**
  - Hospitalized patients
  - Patients with severe or progressive illness
  - Patients at high risk for complications
- **Decisions about antiviral treatment should not wait for laboratory confirmation of influenza**
  - And should not be made on the basis of a negative RIDT
- **Clinical benefit is greatest when antiviral treatment is initiated early, but treatment initiated later than 48 hours after onset can still be beneficial for some patients**

Additional Information

- Summary of Influenza Antiviral Treatment Recs for Clinicians: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
- Interim Guidance for Influenza Outbreak Management in Long-Term Care Facilities: https://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm
- Prevention Strategies for Seasonal Influenza in Healthcare Settings https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm
- FDA Influenza (Flu) Antiviral Drugs and Related Information (including package inserts): http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm
- CDC Free Resources: https://www.cdc.gov/flu/freeresources/index.htm
- American Academy of Pediatrics (AAP) Information on Influenza in Children: www.aap.org/disasters/flu

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  - Influenza Genomics Team
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- **CDC, National Center for Health Statistics**
- **State, county, city, territorial health departments and public health laboratories**
- **U.S. World Health Organization collaborating laboratories**
- **National Respiratory and Enteric Virus Surveillance System laboratories**
- **U.S. Outpatient Influenza-Like Illness Surveillance Network sites**
- **FluSurv-NET surveillance hospitals**
- **World Health Organization, FluNet**

Thank You

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- **Using the Webinar System**
  - Type your question in the Q&A Pod
  - Press “Enter” or click the speech bubble to submit your question

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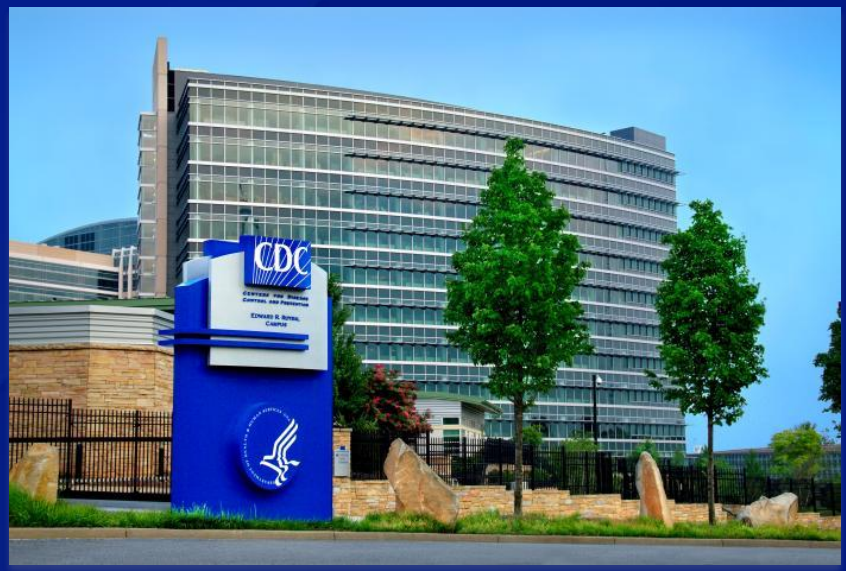
  - Press Star (*) 1 to enter the queue
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question

Thank you for joining!



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